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16. ABSTRACT

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In planning a research strategy, four primary points should be included: (1) Define the most likely clinical changes associated with known or suspected mechanisms or toxicity. (2) Describe the concentrations and distribution of the most toxic environmental agent in the biosphere. (3) Describe fully the population at risk and (4) Evaluate potential cotressors.

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Developing a Health Standard from Epidemiological and Clinical Data

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In: IMPACT OF ENERGY PRODUCTION ON HUMAN HEALTH - AN EVALUATION OF MEANS OF ASSESSMENT, ERDA SYMPOSIUM SERIES 39, 51-59, 1976

ABSTRACT. The problem of environmental health hazards has only recently been given the serious attention it deserves in man's rapidly expanding industrial society. The U. S. Clean Air Act provides the first systematic approach to evaluate health effects of air pollution. But assessing the influence of environmental factors on human health has proved to be a complex problem for researchers, for humans are not uniformly susceptible to environmental influences.

The diseases most likely caused in part by environmental factors are the great modern killers: chronic lung disease, heart disease, and cancer. Because of the complexities of these disease processes, environmental scientists must caution those turning human health effects data into control policy that there is still much ambiguity in these health data.

Tools used to assess health effects of environmental pollution include epidemiology and clinical environmental research.

In planning a research strategy, four primary points should be included:

1. Define the most likely clinical changes associated with known or suspected mechanisms of toxicity.

2. Describe the concentrations and distribution of the most toxic environmental agent in the biosphere.

3. Describe fully the population at risk.

4. Evaluate potential costressors.

All human activity is associated with a degree of stress and with a degree of risk to the public health and welfare. Only recently, however, has man begun to seriously contemplate the degree of stress and risk associated with rapidly evolving technology. Initially these concerns were focused directly at the most obvious site of risk, the workplace itself. Now, these concepts of industrial hygiene and medicine are serving as an important basis for development of the more general field of environmental medicine. As technology increases in complexity, the problems of environmental medicine become more complex, and regulatory decisions based on consideration of environmental health have increasingly important social consequences.

Modern man is well aware of many stresses and health hazards with his rapidly evolving industrial society. These concerns have been expressed in a variety of laws and regulations designed to assure occupational safety and consumer protection over the past several decades. Only relatively recently, however, has a serious attempt been made to protect the general population from harmful effects of existing and emerging industrial and technological processes.

The impact of industrial and residential emissions and effluents on society at large has long been recognized. Conversion from burning of soft coal for domestic space heating has changed the quality of air not just in the cities of Great Britain. More impressive, the climate of the entire British Isles has been changed. However, the improvement of local or regional conditions, for example with tall stacks, may cause increased acid rainfall or heavy-metal residues in biota thousands of kilometers away. These complex interactions of environmental factors, not only on local and regional populations but on a national and international scale, have focused attention on the necessity for a systematic approach to the evaluation of environmental health hazards. The U. S. Clean Air Act, with its amendments, specifically directs that acquisition of health effects data be expedited to provide the basis for environmental quality standards:

Sec. 103 (i)

(1) In carrying out research pursuant to this Act, the Administrator shall give special emphasis to research on the short-term effects of air pollutants on public health and welfare. In the furtherance of such research, he shall conduct an accelerated research program

(A) to improve knowledge of the contribution of air pollutants to the occurrence of adverse effects on health, including, but not limited to, behavioral, physiological, toxicological, and biochemical effects; and

(B) to improve knowledge of the short- and long-term effects of air pollutants on welfare.

(2) In carrying out the provisions of this subsection the Administrator may

(A) conduct epidemiological studies of the effects of air pollutants on mortality and morbidity;

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(B) conduct clinical and laboratory studies on the immunologic, biochemical, physiological, and the toxicological effects including carcinogenic, teratogenic, and mutagenic effects of air pollutants;

This legislation reflects widespread public concern and has resulted in a major research effort to define the human health effects of many environmental pollutants. Assessing the influence of environmental factors on human health, however, is a complex problem. Definition of public health and description of statistically significant deviation from the norm are complicated by the many factors determining the health status of any population. Association of changes in health status with changes in environmental factors is made even more difficult by the complexity of environmental stress in general.

Adequate dosimetry of environmental factors is essential. The pollutant concentration gradient, ranging from background through levels actually occurring in varying geographic areas to those levels recognized as producing overt toxicity, must be measured unambiguously and accurately for population studies and reproduced in controlled environmental laboratories for toxicological and clinical studies.

Humans are not uniformly susceptible to various environmental influences on their health. This normal range of susceptibility must be recognized when characterizing the population in an epidemiological study, when establishing criteria for subject selection in a clinical study, or when preparing animal models of human disease.

Just as there is a range of susceptibility within the population, there is a spectrum of response within each more or less susceptible subset of the population. The range of response is usually a function of pollutant concentration, duration of exposure, and the presence of cofactors such as exercise, thermal stress, or other pollutants.

Those diseases most likely to be caused in part by environmental factors have, themselves, a multifactorial etiology. They are also the great modern killers and are responsible for a large fraction of human disability and suffering. The cause and natural history of these three major categories of disease (chronic lung disease, heart disease, and cancer) are still very poorly understood. Thus the complexity of describing environmental covariants is compounded by the complexity of the disease processes most likely related to the environment. For these reasons, environmental scientists must continue to caution those responsible for transforming human health effects data into industrial control policy, that those health data will continue to be fraught with much more ambiguity than we wish were the case.

DOSE–RESPONSE RELATIONSHIPS

The pollutant concentration levels in the environment must be accurately and unambiguously measured to determine what association exists between an environmental agent and any putative health effect. This rather self-evident prerequisite to health effects studies is frequently not met. Conceptually simple, it is in practice often very difficult to measure population pollutant dose with acceptable accuracy. This problem is compounded when the agent exists in several forms in the environment and enters the human organism through a variety of pathways and from a variety of sources. Even when good chemical analysis is possible, determination of the actual dose delivered to the individual is difficult. Environmental monitoring at a particular point gives a relatively poor estimate of the fluctuation of pollutant concentrations within the area, and the time course of an individual in that area is even more indeterminate.

Some materials, such as heavy metals and persistent organic compounds, accumulate in human tissue. That accumulation serves to integrate total dose over a period of time and can be expressed as *pollutant body burden*. The total body burden, or distribution within body tissues or physiological compartments, does not differentiate the relative contribution of multiple pathways of entry, nor does body burden usually correlate well with resultant health effects. In general, measurement of the dose of any environmental pollutant an individual receives is still technically difficult.

Measurement of health effects attributable to environmental pollution is also fraught with many methodological difficulties. The definition of *health* and the description of statistically significant deviation from the norm are greatly complicated by the multitude of factors that determine the health status of any population. In general, we define *threshold* as that point where ignorance concerning the health effect of a substance becomes demonstrable. All available data fail to show any significant dose–response relationship below the threshold level. In most cases the threshold phenomenon is a statistical artifact that does no more than identify objectively the level at which our uncertainty of the dose–response relationship begins. Historically, though, the more data accumulated, the lower the threshold becomes. In this context, threshold of effect becomes an operational definition. It simply means, "This is our level of uncertainty concerning the true dose–response relationship as described with available data."

As the tools for measuring dose and health effect are improved, it becomes possible to describe a continuum of effect down toward zero dose. Thus any very small amount of environmental stress has a very small, but measurable, impact on human health. The question is no longer "What is a safe level?" Rather, the question "What level of risk is acceptable?" is raised. The concept of Threshold Limit Value (TVL) is replaced with the much more complicated one of cost–benefit analysis, or definition of acceptable risk. It is no longer sufficient for the scientist to provide a threshold value and suggest a margin of safety. He must provide the decision makers not only with an objective description of health effect as related to dose but also with an estimate of his degree of uncertainty concerning that relationship.

ENVIRONMENTAL COSTRESSORS

Implicit in the description of dose and effect is a relative priority ranking of the described relationships. Although the health effects of a particular environmental agent may be well described, the relative importance of that risk factor compared to other environmental costressors must be determined before a comprehensive control strategy can be established. These environmental risk factors in determining human health must be placed in perspective with other public health risk factors in general. What is the relative contribution of a particular environmental agent with respect to other factors of eating, drinking, smoking, activity, and mode of life in general? So that the finite resources of society to abate these stresses can be employed efficiently, the cost–benefit ratio, not just with respect to industrial pollutants, but with respect to public health in general, must be minimized.

It is well known that smoking increases the risk of industrial asbestosis. Ionizing radiation in some forms, smoking, and asbestos fiber inhalation are all associated with various types of lung cancer. Yet, we are totally ignorant of the relative contribution of these factors, much less the possible interactions among all three of them. More recently, we are beginning to suspect that low-level lead intoxication and certain kinds of ionizing radiation may act synergistically to produce some forms of mental retardation. We are only beginning to explore the relative importance of environmental costressors.

RANGE OF SUSCEPTIBILITY

Humans are not uniformly susceptible to environmental stress. The historic episodes that first drew worldwide attention to the lethal consequences of severe air pollution affected primarily the very young, the aged, and the infirm. Those early observations were evident even to the untrained. Since then, more careful documentation of range of susceptibility has been possible.

In epidemiological studies, greater correlation between pollutant gradient and health effects has been seen in the incidence of respiratory infection in children, in the excess number of asthma attacks, and in excess symptoms in people with cardiopulmonary disease.

Ionizing radiation is known to have an especially deleterious effect on the developing mammal, but we have no firm evidence that any subsets of the adult population are particularly susceptible. Excessive lead intake, by whatever pathway, is associated with impaired central nervous system development in young mammals and may be particularly harmful to people of all ages with some types of kidney disease. Persons with coronary artery or peripheral vascular disease are known to be much more susceptible to low concentrations of carbon monoxide.

SPECTRUM OF RESPONSE

Whereas there is a range of susceptibility within a population, *spectrum of response* refers to the various ways an individual can manifest the effects of environmental stress. The range of response is usually a function of pollutant concentration, duration of exposure, and the presence of costressors such as exercise, thermal stress, or other coexisting pollutants. We have somewhat arbitrarily classified the spectrum into categories ranging from the mildest to the most severe: (1) pollutant body burden, (2) changes of uncertain significance, (3) pathological changes, (4) morbidity, and (5) mortality. Because the proportion of any population falling into any category is greatest with category 1 and least with category 5, it is evident that the concept of "range of susceptibility" is closely related to that of response spectrum. Consideration of the two concepts allows the construction of a three-dimensional dose–response relationship which can be used to calculate risk factors that reflect the degree of hazard as well as size of the population at risk. This kind of prediction is the final goal of environmental health effects research. We are trying to answer the question, "How many individuals in each category of our population are subjected to what levels of risk for a given range of pollutant concentration?"

EPIDEMIOLOGY

The earliest observations of catastrophic results of air pollution were epidemiological. Excess mortality associated with the historic Meuse Valley and Donora episodes was evident even to untrained observers. Since then, epidemiological assessment of environmental health effects has become much more sophisticated and has provided many of the available data on this topic. Such information is most relevant because it relates health effects in humans to what is actually happening in the environment. There is no extrapolation from animal data; there is no simulation of environmental conditions. There are three major problems in environmental epidemiology, however. Because one is studying humans moving about their natural habitat, it is difficult to measure the dose of a particular pollutant they may actually receive. Dose estimates of air pollutants can be calculated from aerometry data obtained in the general vicinity of the study population, but confidence intervals around these estimates are usually large. Dose estimates from other sources such as food and water are equally difficult to determine. The second problem is measuring the health effect, and the third is disentangling these observations from other coexisting and uncontrollable environmental covariates such as occupational exposure or meteorological conditions.

In dealing with the large numbers of people needed for good epidemiology, researchers usually do not have the means necessary for very sophisticated investigation of the health status of their subjects. Even when the means are available, there are serious logistical problems in processing large numbers of people from widely separated areas through specialized laboratory facilities. In the future, some of these difficulties may be overcome with the use of specially designed mobile physiological laboratories. Be-

cause of the relative crudeness of dose estimates and the inability to quantitate subtle changes in health status, it has not usually been possible to derive dose–response relationships from epidemiology data. In spite of these limitations, epidemiology remains a very important source of environmental health effects data and provides many insights for the design of clinical research. In some cases, especially in the study of carcinogenesis, mutagenesis, or teratogenesis, the use of human subjects is impossible, and information from animal studies or epidemiological observations is all we have. Although development of new techniques and concepts, as well as modification of old ones, is making possible more research involving human subjects, exhaustive toxicological evaluation must always precede the clinical studies.

CLINICAL ENVIRONMENTAL RESEARCH

The term *clinical* in this context refers to the use of humans as subjects of environmental health effects research in a laboratory setting such as one finds in a university teaching hospital. It does not necessarily imply, but neither does it exclude, use of hospital patients. The *sine qua non* of clinical research is protection of the rights and safety of the human subjects. It is incorrect to say that experiments with humans can be performed with no risk. All human activity involves risk. The wheels of commerce and industry cannot begin to turn without a certain measurable hazard for the human participants. What is essential is an accurate estimate of that risk and its reduction to a level acceptable to the individual and to society. Experiments must be designed so that any risk is comparable to that which the subject normally incurs in his day-to-day activities. This degree of risk must be accurately and fully explained to the scientist's disinterested but competent colleagues who, in a sense, pass judgment as representatives of society at large. This we call peer review. Finally, the subject himself, usually unsophisticated in matters of research, must have the experiment and the risks explained to him so carefully that he fully understands what is happening to him and accepts with no hesitation and under no duress whatsoever. This we call informed consent.

Inducement to participate in such research must be used with caution so as not to influence the subject's sound judgment. The most scientifically, morally, and socially acceptable inducement is the likelihood that the subject's health may actually be improved as a result of his participating in the research. By this we usually mean that information will be gained that may improve management of a clinical condition, or a risk factor may be identified that can result in modifying the subject's life style to his eventual benefit. Monetary reward should be used only to the extent that it reimburses the subject for time and inconvenience and is not a recompense for undue risk. One inducement that is often neglected or underestimated is simple altruism, or the satisfaction the subject experiences from participating in a worthwhile endeavor that may benefit humanity as well as himself.

There are three important factors in maintaining an acceptably low level of risk in clinical research. First, the environmental factors and contaminants should be held to a level of intensity actually encountered in some areas. In other words, one should reproduce conditions under which many people are living anyway. This tends to minimize the risk as well as make the experiment relevant. Second, great care must be exercised in simulating the environmental condition. The analytic chemist must be sure he is measuring what he thinks he is measuring in the environment. The engineer must reproduce that environment, or components of it, as faithfully as technically possible. The engineer and chemist working together must design a feedback (or fail-safe) control system that provides accurate monitoring of the controlled environment. When the feedback system malfunctions, as it surely will, then it must do so in a way that reduces the level of pollutant and alerts the investigator. Third, the human subject's response to this controlled environment must be monitored throughout the course of the experiment. It is not enough to know what has happened when the experiment is over. The investigator must be constantly apprised of the condition of his subject even while the experiment is in progress so that he can alter conditions or even stop the experiment if desired. Ideally, this "real-time" data acquisition and processing will not only assure the safety of the experiment but will improve the quality of information obtained.

INTERACTION OF POPULATION STUDIES AND CLINICAL STUDIES IN THE DEVELOPMENT OF ENVIRONMENTAL STANDARDS: OXIDANTS, A CASE STUDY

Does the current U. S. Ambient Air Quality Standard for photochemical oxidants (160 $\mu g\ m^{-3}$ maximum 1 hr concentration) adequately protect, with a reasonable margin of safety, the public health? The U. S. Environmental Protection Agency (EPA) has in progress a comprehensive research program designed to provide the answer to that question. Studies in humans, on which the current standard was based, demonstrated the deleterious effects of photochemical oxidants on resistance to respiratory infections, respiratory tract and eye irritation, exacerbation of symptoms in persons with chronic lung disease, decrement in lung function, and impaired exercise performance. Studies of animals corroborated these findings and, in addition, suggested that increases in cytogenetic abnormalities and fetal wastage, as well as interference with immune mechanisms, may occur with exposure to levels of ozone occurring in ambient air. Current research is continuing to explore the influence of photochemical oxidants on the respiratory disease experience and exacerbation of symptoms in healthy and susceptible populations. Clinical studies are evaluating several other health parameters.

Mechanisms of Toxicity

Ozone is known or suspected to exert its deleterious effects by a variety of mechanisms. These effects may be

separated conveniently into two categories: (1) those resulting from the action of ozone as a direct respiratory irritant and (2) those associated with the ability of ozone to act as a generator and propagator of free radicals or other reactive molecules such as aromides. Some of the earliest research in ozone toxicology described alterations in the mechanical function of lung associated with acute exposure. These were expressed as decrements in vital capacity, forced expiratory volume (FEV), flow rates, and airways resistance. Changes of this nature could be expected if ozone acted as a nonspecific upper airways irritant to initiate a neurogenic response resulting in small airways constriction. Alternately, the direct action of ozone on respiratory mucosa with even a minimal resulting edema would be associated with narrowing of the small airways leading to the observed change in lung mechanical function. Although there is a paucity of data associating changes in cardiac performance with ozone exposure, one would expect a cardiac effect secondary to the change in lung function, especially in persons already suffering cardiac impairment because of preexisting illness. Changes in small-airways dynamics, as well as alterations in the mucociliary clearance mechanisms, would explain at least part of the increased respiratory illness experience associated with chronic photochemical oxidant exposure in populations.

It is quite likely that ozone serves to generate and propagate free radicals and/or other reactive molecules in biological systems. Initiation of the sequence of events resulting in formation of these reactive compounds would explain observed changes in the integrity of the organism not directly associated with the effects of ozone on the respiratory system. One would expect that free radical generation could result in changes in nucleic acid synthesis, alteration in protein structure, and interference in the function of cell and organelle membranes. An interference with nucleic acid synthesis could result in cytogenetic alterations similar to those associated with carcinogenesis, mutagenesis, and teratogenesis. By the same mechanism one could anticipate an alteration in cellular immune status. Oxidation of protein cross-linkage would result in the observed chronic effects on lung structure as well as function. Similar changes in antibody structure would account for the postulated impairment of humoral immune status. Metabolic effects such as changes in serum enzyme levels associated with a specific organ damage could also be expected as a result of alteration in the protein structure of the cellular proteins or the enzymes themselves. It is known that ozone exposure can result in peroxidation of lipoprotein cellular membranes. Such changes might be expected to cause a decrement in cellular immune status such as that associated with chemotactic or phagocytic activity. Alterations in cell membrane function resulting in leakage of intracellular contents could be expected to result in elevation of certain serum enzyme levels. Oxidation of red blood cell membranes may interfere with oxygen-carrying capacity, which in turn could impair the central nervous system and cardiac performance.

With these possible mechanisms of toxicity in mind, we have designed a research strategy to evaluate the findings of significance for man of repeated exposures to low levels of oxidant air pollution.

Planning a Research Strategy

The design of a coherent program to evaluate the human health effect of environmental factors is a complex undertaking. Four of the most important aspects of such a program, however, are the following:

1. Definition of the most likely clinical changes associated with known or suspected mechanisms of toxicity.

2. Description of the concentration and distribution of the toxic environmental agent in the biosphere.

3. Description of the nature, size, and distribution of the population at risk.

4. Evaluation of potential confounders.

The usual techniques of epidemiology, clinical studies, and basic toxicology permit, in varying degrees, an approach to these four aspects of environmental health effects research. The strengths and limitations of the three disciplines are well understood and appreciated. Somewhat less thought, however, has been given to the difficulties encountered in deriving an exposure density function for populations. The basic question is "How many people in various susceptibility categories are exposed to what levels of which pollutants and for how long?" Answering this question is essential to the development of a meaningful human damage function.

The EPA is approaching this problem by developing technology in four separate areas:

1. Environmental monitoring.

2. Regional modeling.

3. Clinical research in controlled environmental laboratories.

4. Application of clinical research methods to population studies.

Improved air monitoring has been achieved through use of more accurate and specific sensors capable of providing measurements with very short averaging times. The use of such principles as chemiluminescence has made possible the development of semiautomated monitoring stations which themselves are directed and calibrated by small on-board computers. These monitoring stations are sited in selected urban locations throughout the United States and feed their data by telephone lines into a command central computer located in our research headquarters in North Carolina. Thus human population exposures in regions where we are conducting health studies can be assessed constantly.

Such monitoring, however sophisticated it is, does not give adequate dose data for the recipient population. Meteorological conditions cause constantly varying pollutant isopleths around the monitoring stations. Use of dispersion models provides a method for better estimation of local pollutant concentrations. These models are validated or improved by mobile monitoring stations that can

make many intermittent analyses throughout a region and by monitoring grids established specifically for that purpose. Because people do not remain stationary in a given region, activity profiles are being developed to model their movements through pollutant gradients. Classic methods of epidemiology, used with these estimates of population dose, have provided the data base for our Community Health and Environmental Surveillance System (CHESS), a systematic assessment of associations between environmental factors and public health. In addition, targeted epidemiological studies designed to answer specific questions are conducted.

Interpretation of data from population studies is fraught with many well-known difficulties. When possible, it is desirable to corroborate the epidemiological findings with those of carefully controlled clinical studies. The standard techniques of the clinical scientist are used to assess transient and subtle changes in the health status of his subjects. Not standardized, however, are the techniques for manipulating and controlling the subjects' environment. Controlled environmental laboratories of relatively simple design have been in use for several years, but just coming into existence is a second generation of these laboratories which will use the same instruments to control the interior environment as are used in our cities to measure the ambient environment. Control mechanisms linked to these monitoring instruments provide the capability for programming diurnal pollutant cycles to simulate those occurring in urban areas.

One of the principles followed in designing clinical environmental studies is that the exposure schedule should not generate a stress in excess of that being placed on large numbers of people breathing ambient air. This principle emphasizes once more the importance of accurate and detailed air-quality data.

Our current clinical studies of ozone can serve as a useful example of how air-quality data are interpreted for experimental design. For example, during 3 months of the year in Glendora, Calif., the daily maximum hourly average ozone concentrations equaled or exceeded 600 $\mu g\ m^{-3}$ about 10% of the time. Thus, on the average, at least 1 hr each day for 36 days that year, people in Glendora were exposed to a minimum of 600 $\mu g\ m^{-3}$ of ozone. But what might have been the peak and hourly concentrations just before and after the daily maximum hourly average? When the maximum hourly average is 600 $\mu g\ m^{-3}$ or greater, peaks may be as much as 100 $\mu g\ m^{-3}$ higher than the maximum hourly average, but preceding and succeeding hourly concentrations could be 100 $\mu g\ m^{-3}$ or more lower. An automated air monitoring system provides much more rigorous analysis of such exposure profiles for purposes of calculating population damage functions and designing controlled environmental studies.

Epidemiology

Among the features unique to epidemiological studies is the possibility of assessing the effects on free-living human beings in natural (as opposed to simulated) pollutant exposures. Because of the difficulties in quantitating the complexities of pollution exposure profiles, as well as the wide variation of human response, no single study will provide conclusions that can confidently be generalized.

In an attempt to accumulate a credible data base for approaching the questions of how air quality relates to human health, the EPA is currently conducting a substantial epidemiological program that addresses a variety of regulated and currently unregulated pollutants of major concern to the agency. The studies that specifically address the effects of ozone or photochemical oxidants include the following:

The CHESS was designed to provide temporal and spatial replications of a set of standardized studies which related sensitive health indicators to simultaneous measurements of air quality. This program involved seven communities in the Los Angeles Basin which are continuing to serve as sites to test hypotheses generated by the CHESS program.

Although the major emphasis of these studies is directed toward effects of ozone and nitrogen oxides, total and respirable particulates, SO_2, and CO are also considered.

Health indicators used in the population studies can be classified as either effects of short term (i.e., approximately 4 days) or long term exposure. This dichotomy is an oversimplification because it is impossible at present to determine whether long-term effects should be attributed to total integrated exposure or repeated exposures of short duration.

Short-term indicators that have been utilized include increases in symptoms of irritation to the eyes and respiratory tract during high pollution periods, exacerbation of cardiopulmonary disease in panels of adults, and increases in attacks in panels of asthmatics. Long-term effects include frequency of acute lower respiratory disease in children, prevalence of chronic respiratory disease in adults, incidence of acute respiratory disease in families, and pulmonary function ($FEV_{0.75}$) in elementary school children.

Many investigations of circulating peripheral lymphocytes in populations of persons with histories of exposure to ionizing radiation have demonstrated a radiation dose–cytogenetic response relationship. Other investigations have suggested that exposure to certain drugs and viral infections can cause increases in the proportion of abnormal cells in peripheral lymphocytes. Animal studies have indicated that ozone may be a particularly potent chromosomolytic agent. Because ozone is the primary constituent of photochemical oxidants, it is of interest to determine whether or not a higher proportion of populations exposed to this type of air pollution carry aberrant cells than the nonexposed. It is also of interest to determine whether or not a continual increase in the proportion of aberrant cells occurs and, if aberrant cells are induced, whether or not the process is reversible.

Samples of blood were taken from 150 freshmen entering the University of Southern California. The samples were collected as soon as possible after the students arrived for registration. Half of the samples were from students who have never lived in the Los Angeles Basin, and half were from students whose homes are in the Basin. The Los Angeles students were matched to the non-Los Angeles students by sex and college domicile.

With standard techniques, lymphocytes were cultured and 100 cells scored for a study of induced aberrations. The analysis included the assignment of each chromosome, of each cell examined, to a given group of the Denver classification, determination of the chromosome number of each cell examined, as well as noting the position on the slide of each chromosomally abnormal cell.

Two additional samples of blood will be drawn and the lymphocytes cultured and scored for each student in the study during the first school year. The second sample should be drawn shortly after the Christmas–New Year break, and the third sample should be taken before the end of the school year.

Analyses will include comparisons of aberration rates in the Los Angeles resident students and non-Los Angeles resident students at each of the three sample times. In addition, temporal analysis of the proportion and types of abnormal chromosomes in each subject will be determined. The same study will be repeated in these students during their sophomore and junior years.

To develop sensible short-term air quality standards requires firm knowledge of human response to acute exposures to unusually high levels of ambient air pollution. Such knowledge should be adequate to answer the following questions for each major pollutant or class of pollutants: (1) Does the pollutant exert effects at concentrations down to zero, or is there a threshold that the pollution concentration must exceed before exerting effects? (2) If there is a threshold concentration, what is its magnitude? (3) Is there a minimum duration of exposure necessary to produce effects? (4) If so, what is the minimum duration? (5) Of the reported human responses to acute pollution exposure, which of them are based on firm and reproducible results?

A good deal of useful knowledge has emerged from epidemiological studies of the effects of acute air pollution exposure. For instance, there is evidence of increased eye irritation and coughing at ambient oxidant concentrations above about 200 $\mu g\ m^{-3}$. Such studies usually have relied on the judgments of subjects, whose precision in reproducing the results may be limited. Thus the knowledge gained from studies to date would be enhanced and amplified by a series of epidemiological investigations of parameters which eliminate such judgmental decisions by the subject.

A study currently under way in the Los Angeles area was designed to minimize the possibility of subjectivity. This study examines four population groups which may represent a spectrum of vulnerability to acute oxidant exposures. At one end of the spectrum are trained runners, who may be most resistant to adverse effects but who may show physiological or biochemical impairments when physically stressed. At the other end of the spectrum are documented asthmatics and chronic bronchitis patients, who may be most sensitive to changes in air pollution levels. Between these extremes are healthy outdoor workers, who, because of their unusually constant outdoor exposures, may reflect acute pollution effects more readily than other healthy segments of the population.

Health data have been collected before, during, and after acute exposures to unusually high ambient air pollution levels. Specific items of health data are electrocardiograms, blood pressure, heart rate, total white cell counts, differential white cell counts (including eosinophils), blood levels of immunoglobulins, and pulmonary function tests. These tests included closing-volume determinations and volume vs. time tracings of the entire forced vital capacity (FVC) maneuver. From such tracings, the FVC, the FEV, the maximal midexpiratory flow rate (MMEFR), the maximal expiratory flow rate (MEFR), and flow-volume loops can all be extracted.

From the outdoor workers and asthmatics, measurements of pulmonary function were obtained on successive days during the season of highest pollution exposure.

Aerometric data, collected continuously throughout the period of study, are available for each study community. For all four groups under study, complete and accurate information has been collected on additional variables, such as age, height, sex, race, smoking habits, socioeconomic status, and occupational exposure to respiratory irritants, which may affect the investigated parameters.

Finally, Los Angeles will be one of several major metropolitan areas in which studies of daily mortality in relation to pollutant exposures are being initiated.

Clinical Studies

To date, most studies investigating effects of ozone in human volunteers in a controlled setting have focused on pulmonary effects. D. V. Bates and coworkers demonstrated decrements in lung function after 1 and 2 hr of exposure to levels of ozone of 740 $\mu g\ m^{-3}$. H. D. Kerr exposed healthy volunteers to 1000 $\mu g\ m^{-3}$ ozone for 6 hr and demonstrated decrements in certain parameters of lung function after 4 hr of exposure to this concentration.

There exists a body of information demonstrating ozone effects on other organ systems in animals. Chinese hamsters, following a 5 hr 400 $\mu g\ m^{-3}$ exposure to ozone, were found to have chromosomal abnormalities in circulatory lymphocytes not found in a control group. These results confirmed previous findings of increased numbers of chromosomal abnormalities occurring in human cells exposed in vitro to 16 mg m^{-3} (8 ppm or 16000 $\mu g\ m^{-3}$) for 5 to 10 min. Other animal studies have found that ozone exerts an effect on phagocytic ability of pulmonary alveolar macrophages after a 3 hr exposure to 1340 $\mu g\ m^{-3}$ ozone. Further studies demonstrated increased susceptibility to

respiratory infections in mice and hamsters following exposures from 2.6 to 8.8 mg m^{-3} ozone.

Proceeding from these results, we have initiated experiments to evaluate the effects of ozone on:

1. Lung function.
2. Chromosomal abnormalities.
3. Lymphocyte transformation.
4. Neutrophil adherence and chemotaxis.
5. Neutrophil phagocytic and killing index.
6. Carcinoma - associated antigen titers.
7. Serum enzyme levels.

SUMMARY AND CONCLUSIONS

Assessing the influence of environmental agents on public health is a difficult multifactorial problem. Composition and concentration, sources, distribution, and bioavailability of pollutants must be determined before meaningful estimates of environmental risk factors are possible.

As improved estimates of existing dose and dose-rate factors are developed, biological effects data become more relevant. Spectrum of response and range of susceptibility provide the tools for establishing a dose–response relationship from which some objective cost–benefit analyses can be drawn. The problem of assessing combined effects due to pollutants of multiple pathways has barely begun. It will be best pursued using firm principles and precedents established in evaluating single-pollutant effects.

Sound toxicological data are the required foundation for developing and testing hypotheses with population studies and clinical studies. As such, they are indispensible. Wherever possible, however, human health data must provide the basis for environmental controls. Careful study design and innovative methodology will assure that human studies can be conducted to give dose–effect relationships for environmental standards that assure the protection of public health without being excessively restrictive.

DISCUSSION BY ATTENDEES

Greenfield: John, I guess we agree with you completely about a well-defined dose–response relationship where you can clearly identify the pollutant and start to establish a cause and effect. What troubles me most is the situation of a multifactorial complex pollutant case, where you are dealing with a surrogate pollutant and trying to establish relationships using that surrogate where the true relationship between the surrogate and what may be a much more complex set of pollutants is not well defined. As you know, this becomes particularly troublesome when you try to control using the surrogate pollutant. Would you like to comment on the use of surrogate in health standards studies?

Knelson: I think what you said is a comment more than a question, and you know that this is a difficult situation. I really don't have a good answer. In the past, though, we have lacked adequate characterization of the complex mix of air pollutants, which you are probably referring to. Although whatever you and I say will apply to any media, we both know that the area of air-pollution control specifically is especially difficult because it is a multibillion dollar control bill for the national economy. The only comment I can make is that the use of surrogates must be minimized increasingly as we improve our ability to describe environmental quality—in this case, probably air quality. If I can add anything to this conversation, it is that I would like to see more and more the adoption of operational definitions for environmental quality. By operational definition, I mean what you get when you do a set of measurements. Then we must begin to control the categories of compounds in the environment using these operational definitions. If you are talking about sulfates, for instance, you can say, "OK, fellows, let's agree that acid sulfate aerosol is what you get when you use this sampler with these size fractionating characteristics, and you do a strong acid titration, and this, and this, etc.; and that is our operational definition of acid sulfate aerosol, and yes, over the next 5 to 10 years, we will refine our measurement technique." It doesn't matter whether you are talking about acid sulfate aerosol, nitrosamine, air, water, or food. I think we have to come up with some accepted across-the-board operational definitions. Otherwise, because these are frequently pacing items in the development of the biological data base, we are simply going to be making capricious decisions with respect to environmental control or pushing that decision into the future in a way that may not be acceptable for the protection of the public health.

Samuels: If I understand you correctly, you are talking about the use of biological data as input into cost–benefit analysis. Is that right?

Knelson: I think that, one way or another, we have to describe what we are buying when we pay something for environmental control.

Samuels: But as a biological scientist rather than as a social scientist, first, are you sure you understand what a cost–benefit analysis is as exemplified by the typical microeconomic analyses done by the government, and, second, are you sure that it is the appropriate and only mechanism?

Knelson: It is far from being the only mechanism, and I don't pretend to understand the intricacies of cost–benefit analyses from the viewpoint of the professional economist. I am not only a biologist but a consumer, a voter, and a taxpayer, and I would like to have some idea of whether putting on a catalytic converter or paying for a microcomputer to get lean burn, putting up tall stacks, or using intermittent control strategy will increase the cost of a kilowatt of electricity, or how much it will increase the cost of a plastic product (i.e., what am I getting in terms of improvement of my longevity, improvement of my ability to enjoy the years I am going to live). We all know that environmental factors are not overwhelming in the definition of public health, that there are other things which make you get sick and die. In the past, environmental health factors have been totally neglected. There has been no real field of environmental medicine in the past, and so

now these factors must be quantified in some way and ranked with the other risk factors. I know that developing coronary artery disease is related to my life style, my level of activity, and whether I eat too much or drink too much; however, development of coronary artery disease is also impacted by some environmental factors over which I don't have any control, and I want to know where they rank and how much I am going to have to control them.

Samuels: If I understand correctly, you are defining or establishing a system of biological analysis that fits within a broader system of social analysis; but you are not sure what that system of social analysis is?

Knelson: There are many answers I don't have, but I am groping for a few.

Ravenholt: We have wrestled with the problem of air pollution standards, setting what would be the highest standards in the country in terms of sulfur dioxide emission and particulates as applied to the Mojave, Southern California Edison plant which, when the prototype and other experiments on alternate methods of achieving the standards are accomplished, produces a price tag that may be close to $200 million to retrofit adequately the plant at Mojave for these standards. This finally connects with the rate to the consumer and with his decision-making process of what is to be the balance between the achievement of the technological standard and the cost benefit. This impact reached the state legislature this year, and its action was a 2-year moratorium on the enforcement of this compliance plan until further assessment of the balance could be made. The point to address is the one for which we have no one good answer, because we have been using the requirement of demonstrating an absence of impact on the ambient air as the central criterion of permissible function in a given mode, and we have to move on from that with the threshold shifting downward as the sophistication of measurement improves. We must move to a combined judgment of the cost-benefit impact on the human and other key elements, and I can only identify the cost impact that we are appreciating now as we see the standards that we set come into contact with the true cost of achieving them on large operations.

Knelson: I would like to make just a remark on your comment. That is, we have a lot of uncertainty in life, and many times we have to gamble. You say it is going to cost $200 million to do something, but that doesn't mean a thing to me. There is no frame of reference for that $200 million. I don't know if it will increase the price of a kilowatt-hour of energy one cent or a fraction of a cent for the user. There is a time when, if you have a certain level of anxiety about a potential health effect, you must be willing to gamble, and it is the end user you have to look at. If we are controlling vinyl chloride and it is going to cost us many hundred millions of dollars to control it, the user has to decide if it is OK to pay another cent for a phonograph record just because vinyl chloride *might* be an important environmental carcinogen. I don't care whether it costs $200 million or a zillion dollars for the industry, it has to be translated into something that the final end user can understand. He has to gamble on it because we don't have the answers, but we do have the inadequacies that Shelly Samuels has mentioned. OK, it is going to cost $200 million for that plant. Johns Manville decided that it was economically unfeasible to reduce amphibole levels to a certain degree in its manufacturing process, but it was absolutely economically feasible to move the corporate headquarters from the East Coast to Colorado. These are societal decisions that have to be made; the end user's dollar value vs. putative health effect or perhaps known health effects, in some cases, must be balanced.